

# Computational Toxicology Framework Overview

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Office of Research and Development

# Computational Toxicology Framework Overview

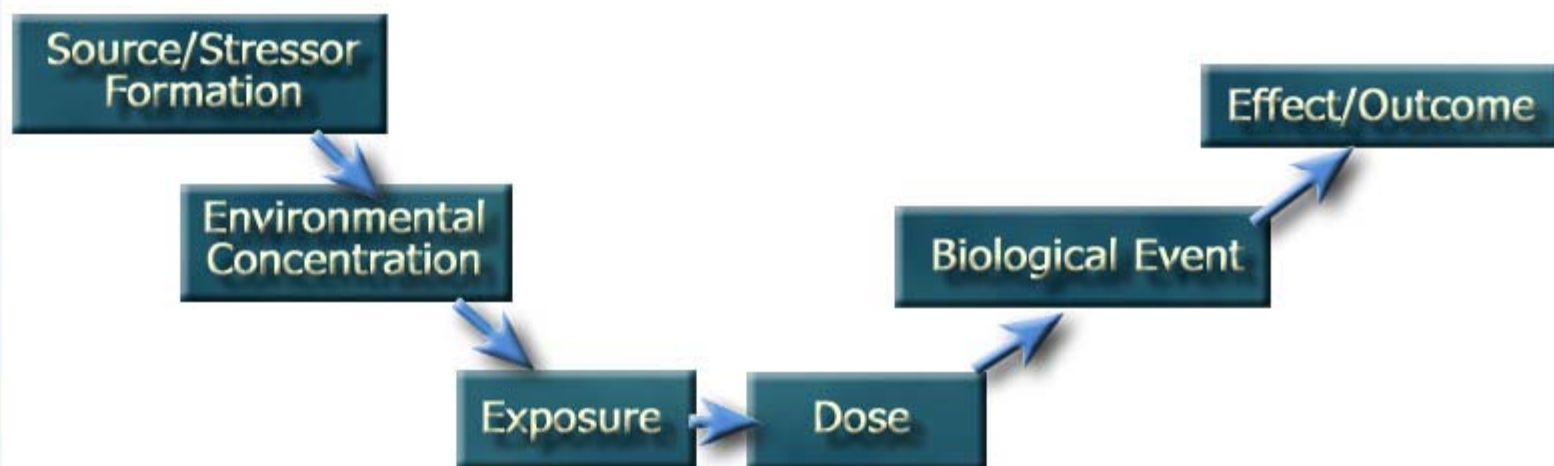
## Outline

- EPA's Science Policy Council Interim Policy
- EPA Context for Comp Tox Program
- Challenges
- Framework

# Science Policy Council's Charge

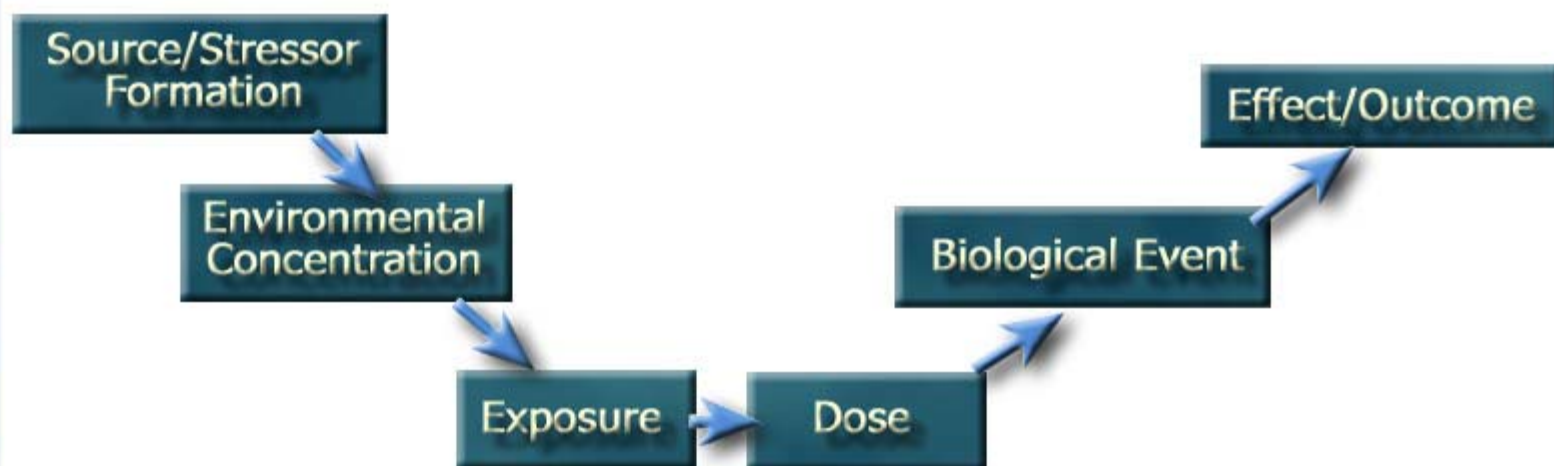
- Develop Interim Policy
- Develop an Action Plan to address technical and policy challenges for appropriate use of genomics technologies and data in EPA

EPA Interim Policy encourages and supports continued genomics research as a powerful tool for understanding the molecular basis of toxicity and developing biomarkers of exposure, effects, and susceptibility



## EPA Context: Quantitative Risk Assessment/ Risk Management for Priority Pollutants

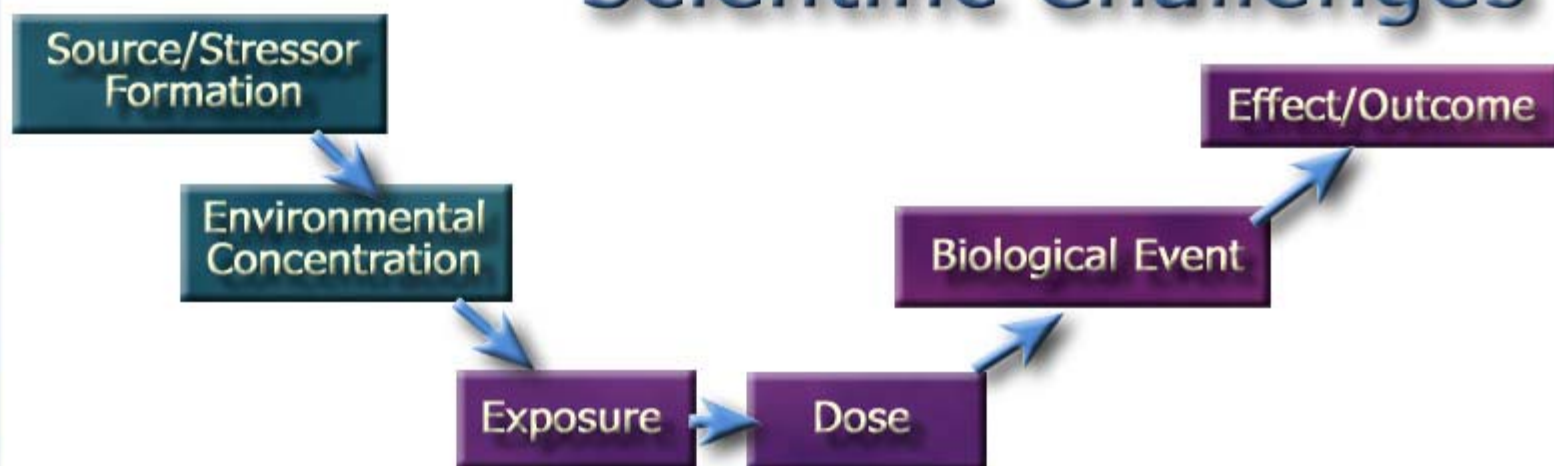
- Methods to Detect & Characterize
- Evaluate Single Chemical at a Time



## PROGRAMMATIC CHALLENGES

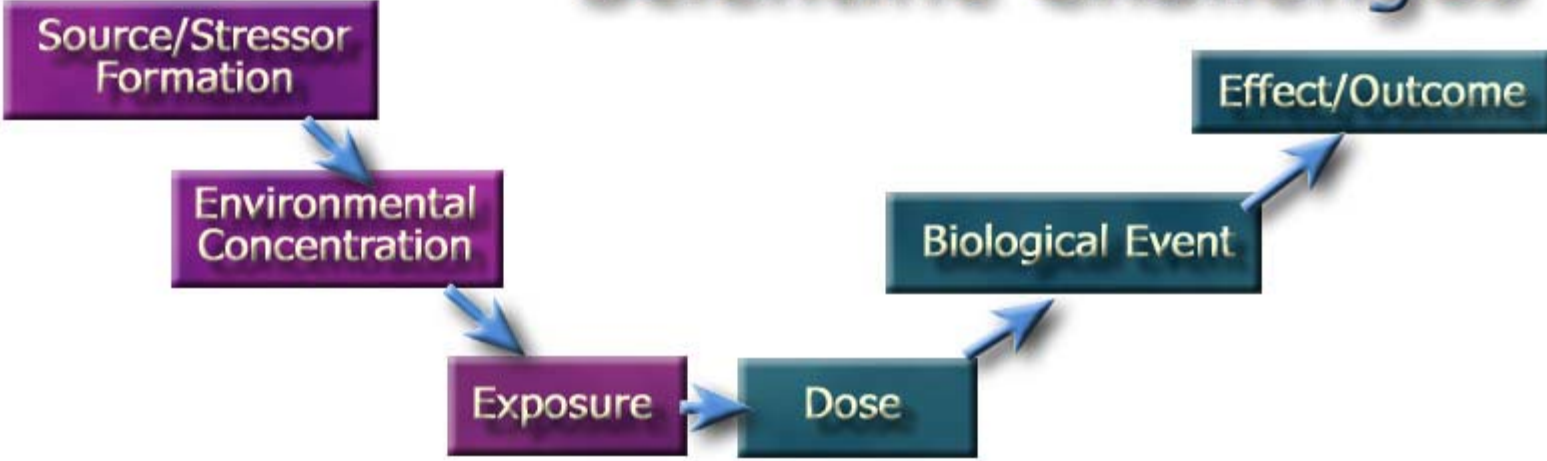
- Many Priority Lists Already in Queue (e.g., EDC's, Pesticide Inerts, HPV's, CCL) with No Risk-Based Criteria for Setting Testing Priorities
- Different Authorities – Different Testing Requirements with No Scientific Basis for Flexible Testing Approaches
- Lack Data Needed to Reduce Uncertainties by Quantitative Risk Assessments (e.g., extrapolations)

# Scientific Challenges



- Delineate Toxicity Pathways
- Extend Cross- and Within-Species Extrapolations
- Identify Endpoints for QSAR Models

# Scientific Challenges

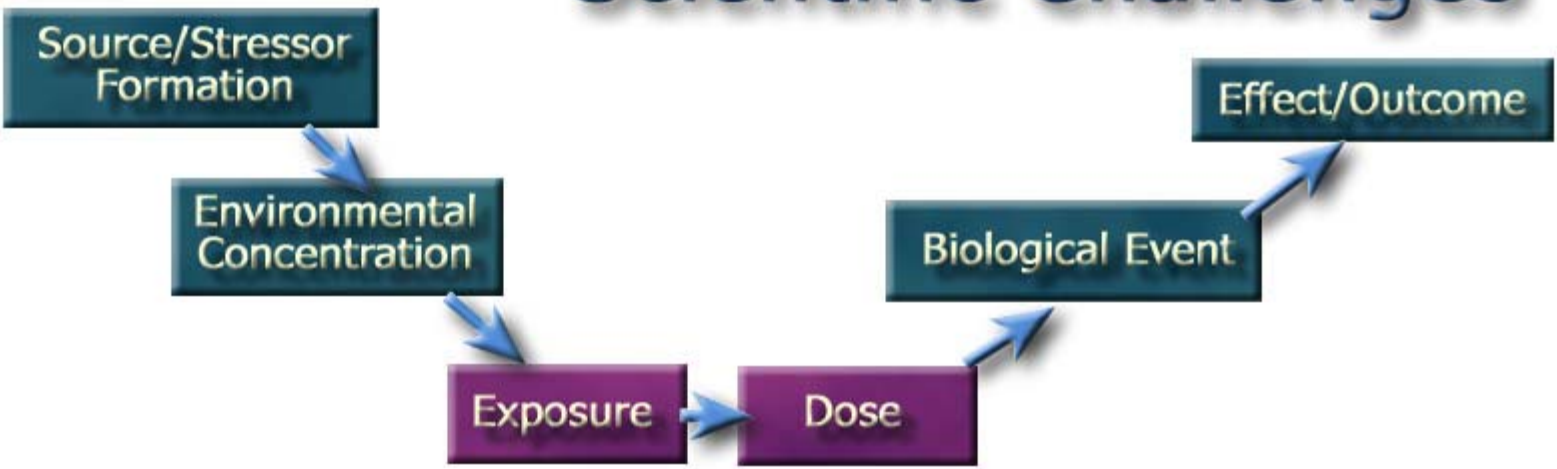


- Exposure Biomarkers
- Fate/Transport Models
- Exposure Models



*Building a  
scientific  
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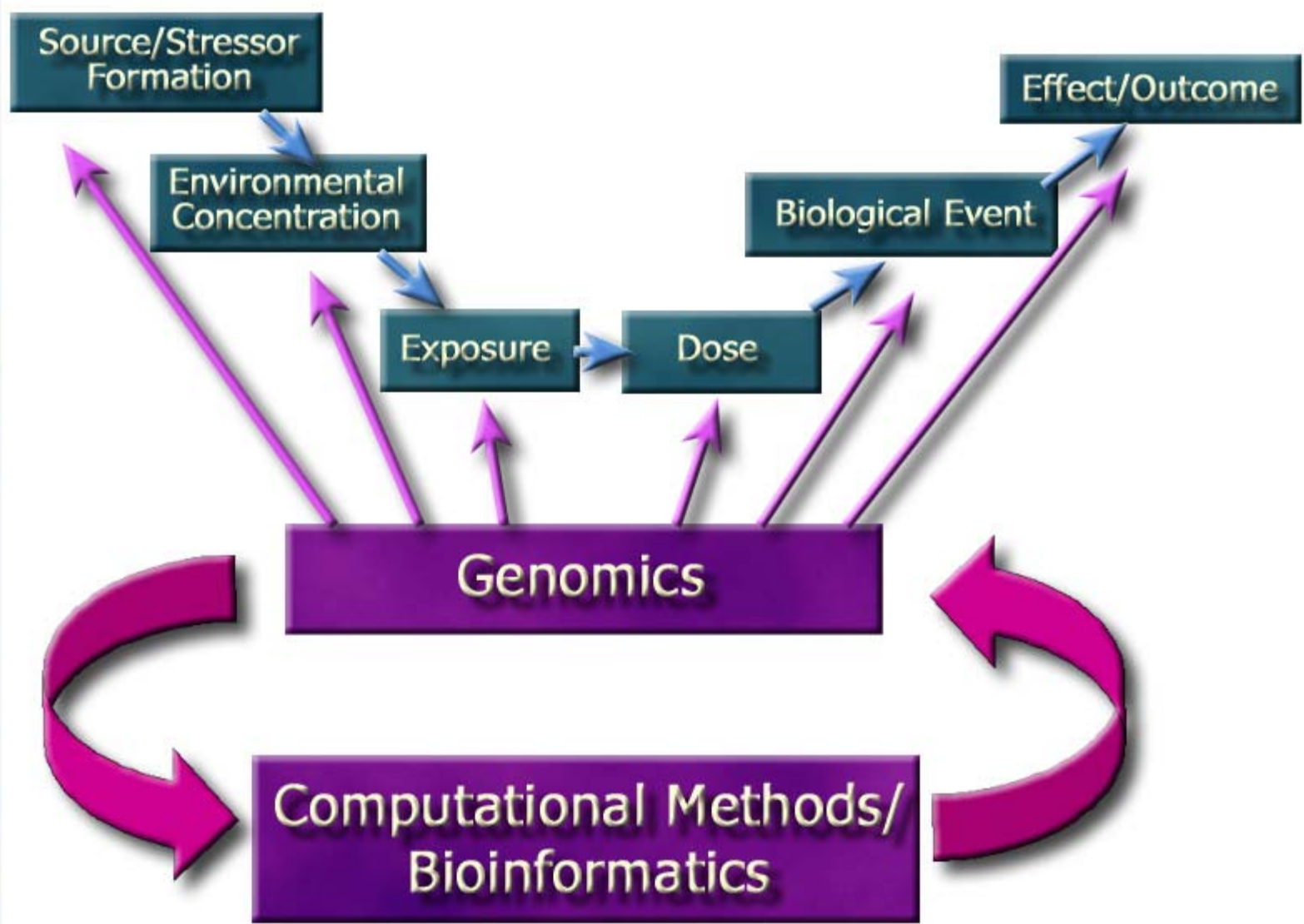
# Scientific Challenges



- Dose Metrics
- Understanding Cross- and Within-Species Variations in Pharmacokinetics



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To integrate modern computing and information technology with the technology of molecular biology and chemistry to improve EPA's prioritization of data requirements and risk assessments for toxic chemicals

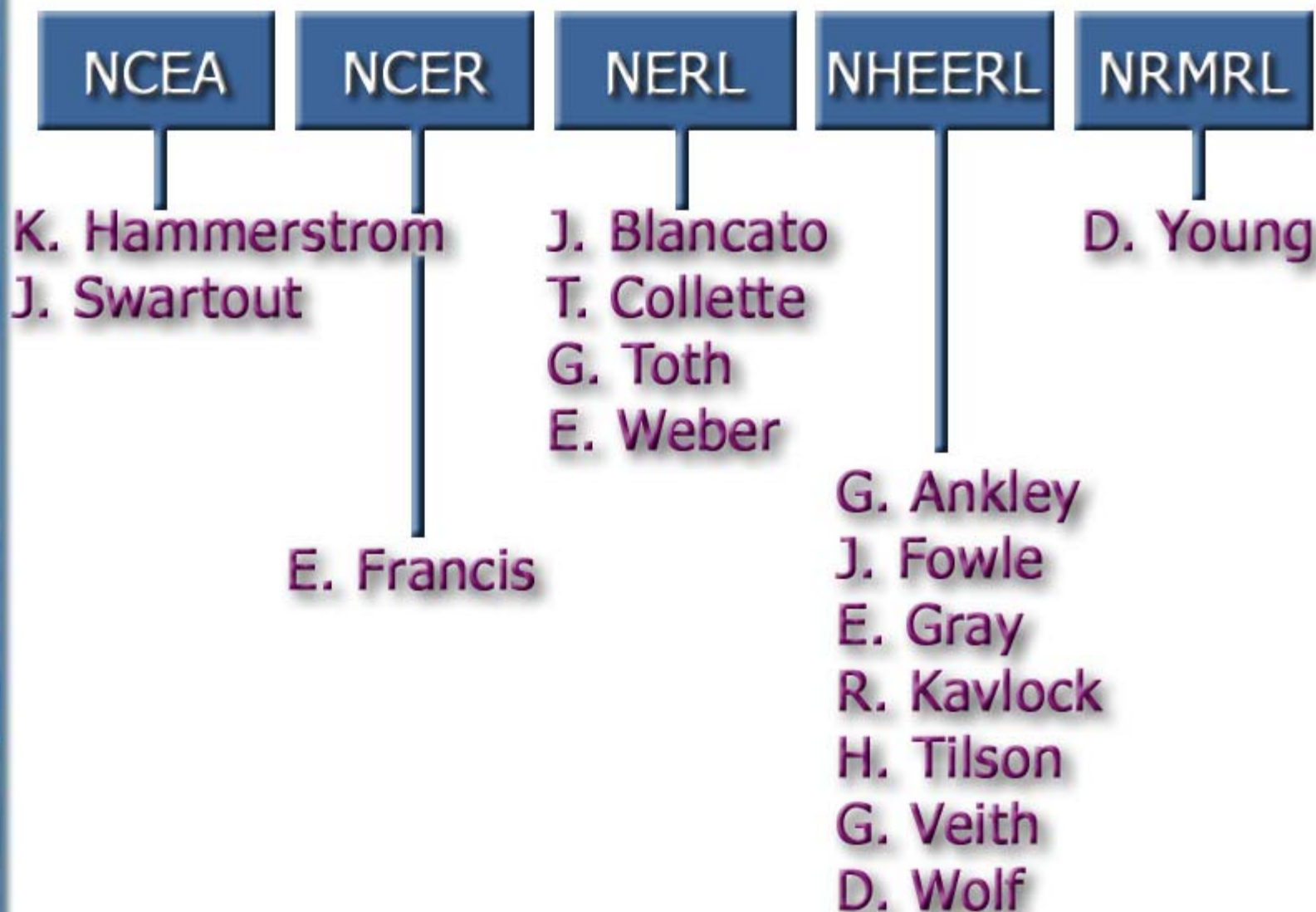


# ORD Technical Design Team

- Formed in late 2002
- Consists of representatives from five ORD Labs/Centers
- Charged with drafting Framework for a Computational Toxicology Research Initiative within ORD



# ORD Design Team



# Overarching Themes

- A technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions within EPA
- Build the capacity to prioritize, screen and evaluate chemicals by enhancing the predictive understanding of toxicity pathways
- Success measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern

# General Objectives

- I. Improve linkages in the source-to-outcome paradigm
- II. Provide predictive models for screening and testing
- III. Enhance quantitative risk assessment

# I. Source to Outcome Linkages

- Chemical transformation and metabolism
- Diagnostic/prognostic molecular indicators (Exposure and Effects)
- Dose metrics
- Characterization of toxicity pathways
- Metabonomics
- Systems biology

## II. Predictive Models for Hazard Identification

- QSAR approaches
- Pollution prevention strategies
- High throughput screening

### III. Enhancing Quantitative RA

- Applying computational methods in quantitative risk assessments
  - Validation and development of protocols
  - Defining responses
  - Modifying Uncertainty factors
- Dose response assessments
- Cross species extrapolations
- Chemical mixtures

# SUMMARY

- Completed Framework to guide development of research program
- Successful implementation will pose a number of challenges
  - Prioritization/Engagement
  - Coordination/Collaboration
- Workshop intended to begin transition from Framework to research program
  - Communicate Framework
  - Identify/foster partnerships
  - Begin to shape research agenda